CEPHALOSPORINS IN ADULT MENINGITIS*

THOMAS R. BEAM, JR., M.D.
Chief, Infectious Diseases
Buffalo Veterans Administration Medical Center
Buffalo, New York

BACTERIAL meningitis in adults is common enough to provide some experience in diagnosis and treatment for most primary care physicians. But it is not common enough to allow critical appraisal of treatment modalities in any single medical center. Collaborative studies, successfully completed in neonates, have not been accomplished in adults. Therefore, data generated from experimental studies in animals have often served to fill the void of controlled clinical trials.

In the treatment of adult bacterial meningitis there is no margin for error. Prompt institution of appropriate antimicrobial therapy can be life saving. Therapeutic progress has been slow, particularly with Gram negative infections, but some improvement in morbidity and mortality may result from the newly developed cephalosporin antibiotics. Documentation of the beneficial impact of these drugs depends on careful evaluation of phase IV (postmarketing) data. Because there is no organized collection of this information, impressions may be tempered by reporting bias rather than legitimate critical appraisal, but the currently prevailing impression is that the new cephalosporins represent a significant therapeutic advance.

GENERAL CLINICAL FEATURES OF ADULT MENINGITIS

Although classical bacterial meningitis has clinically distinct features such as severe headache and nuchal rigidity, the possibility of this disease must be considered well in advance of the appearance of such signs and symptoms. Headache, fever, and altered consciousness provide sufficient grounds to investigate the possibility of a central nervous system infection in older patients. Other clinical clues which should be sought include otitis, sinusitis, head trauma, pneumonia and upper respiratory tract infec-

*Presented as part of the *Symposium on Current and Future Directions in The Use of Antimicrobial Agents* held by the Sections on Medicine, Pediatrics, and Surgery of the New York Academy of Medicine April 19, 1983.

This work was supported by the Veterans Administration.
This symposium was supported in part by a grant from Hoechst-Roussel Pharmaceuticals, Inc.

tions. All can precede meningitis. Additional major risk factors are recent neurosurgery and presence of an indwelling intracranial foreign body, such as a cerebrospinal fluid shunt.

Epidemiologic information can also be helpful. Bacterial meningitis is most likely between January and May (actually during the interval between the first fall and last spring frosts). Viral meningoencephalitis predominates from June to December, and tuberculous meningitis has no seasonal pattern.

Age is also an important factor in suggesting etiology. In one recent series, more than 75% of cases of adult bacterial meningitis occurred in individuals older than 40 years, while 94% of cases of viral meningitis occurred in adults younger than 40 years. Tuberculous meningitis showed no age predominance.[1]

Etiology of Adult Meningitis

The Centers for Disease Control have not established bacterial meningitis as a reportable disease, although meningococcal infections are. Therefore, there is little accurate information on nationwide incidence of meningitis of diverse etiologies. Fraser has evaluated the population of Olmstead County, Minnesota,[2] and Charleston County, South Carolina,[3] to develop estimates of disease occurrence. Major pathogens identified included *Hemophilus influenzae* (estimated national incidence of 9,660 cases per annum), *Streptococcus pneumoniae* (4,830), and *Neisseria meningitidis* (4,370). "Other bacteria" account for an estimated 3,910 cases per annum, based on extrapolation of data from these carefully studied patient populations.

Records were available for review from 1935 to 1970 in Olmstead County. The annual incidence per 100,000 population for all forms of bacterial meningitis increased from 6.3 in 1935-46 to 9.8 in 1959-70. Among adults older than 60 years of age there was a marked increase in cases caused by "unusual" bacteria, including Gram negative bacilli. The median age of patients with meningitis caused by "unusual" bacteria increased from 17.5 to 56 years during the periods studied. Fraser also observed that case fatality rates for these pathogens were high in the preantibiotic era (83%) and remained high through 1970 (64%). Thus, people older than 60 years were more likely to contract meningitis caused by a life threatening organism and more likely to die from that infection.[2]

Recent studies have emphasized the importance of Gram negative

meningitis in certain locales such as New York City, but not in such others as Rochester, New York. Cherubin et al. reviewed the records of the New York City Health Department.[4] Meningitis is a reportable disease in that community. Enteric Gram negative bacilli accounted for 158 cases and *Listeria monocytogenes* for 53 cases during the eight-year study interval. Gram negative bacillary meningitis was more common among septic elderly patients or adults with traumatic skull fracture than among newborns. Mortality was 71.3%. In contrast, a 10-year review of meningitis in Rochester identified 65 cases, 25 of which were attributed to bacterial agents, and only one of which was caused by a Gram negative bacillus (*Pseudomonas aeruginosa*).[5] The explanation for differences in etiologic agents between these two communities is uncertain, but clearly Gram negative bacillary meningitis should be considered in adult as well as neonatal patient groups.

Clinical Syndromes of Gram Negative Meningitis

Haemophilus influenzae[6-8] and *Neisseria meningitidis*[9] occasionally cause meningitis in adults older than 40 years of age. No clinically unique features will reliably identify the etiologic agent, although the petechial lesions of meningococcemia may be helpful.

Gram negative bacillary meningitis may be anticipated in certain settings. Spontaneous meningitis may be community acquired or nosocomial.[10,11] Extraneural foci of infection such as pyelonephritis, endocarditis, and sinusitis or otitis are often found. Treatment directed at the primary site may be insufficient to prevent meningitis. Clinical presentation usually includes acute decompensation in the patient's status along with the classic features of headache, fever, nuchal rigidity, and altered consciousness.

The second group of adults susceptible to this disease includes patients hospitalized following neurosurgical procedures or head trauma. Their clinical presentation is more subtle, and lumbar puncture is often performed to evaluate abnormal mental status in a patient 10 or more days after surgery. The source of the infection is most often a craniotomy wound infection. Patients having more than one neurosurgical procedure during a single hospitalization are particularly at risk. Mortality is less with neurosurgical meningitis than with spontaneous disease.[10,11]

The Role of Animal Models of Meningitis in Predicting Clinical Efficacy

Because relatively few cases of adult Gram negative bacillary meningitis occur at any one medical center, treatment of this disease has often been based on results obtained in experimental animal models. Recent studies have been performed most often in rabbits.

These results have several limitations. The first is the obvious species difference. Second, formation and turnover of rabbit cerebrospinal fluid are more rapid than human. Turnover of drugs in rabbit serum is also more rapid than in humans. Third, the adult animal model requires that organisms be inoculated intracisternally,[12-14] a procedure that mimics neurosurgically-related or trauma-related human disease, but clearly differs from spontaneous infection. Finally, host defenses in the rabbit such as pre-existing antibody and serum bactericidal activity may differ from human defenses. These phenomena may be crucial to the outcome of experimental and clinical infections.[15,16]

With all these limitations in mind, the animal model still provides important information about the kinetics and efficacy of new antimicrobial agents. If a new antibiotic shows good *in vitro* activity against meningeal pathogens and favorable characteristics in the treatment of experimental rabbit meningitis, it is then usually delivered as a single injection to patients undergoing diagnostic studies of cerebrospinal fluid or neurosurgical procedures. This provides limited information on the ability of the drug to penetrate human cerebrospinal fluid. The compound is them piggybacked onto "standard" therapy for patients with meningitis of known etiology or tested where conventional antimicrobial therapy has failed. Additional supportive evidence is provided from these studies to document potential efficacy.

A limited number of patients are then evaluated under controlled conditions, such as the Neonatal Meningitis Study Group endeavors. Based on all this information, the Food and Drug Administration must decide if an approved indication for treatment of meningitis is warranted, and, if so, for which pathogens. Finally, the compound is released for use to all practitioners under circumstances which they deem appropriate. There is no formal data collection system after marketing a compound, known as the phase IV evaluation of the drug.

Results with Agents Other than Cephalosporin Antibiotics

Ampicillin, chloramphenicol, and gentamicin were the mainstays of chemotherapy against Gram negative bacilli causing meningitis until the recent past. Since 30% of *E. coli* causing neonatal meningitis and the majority of strains causing adult meningitis were ampicillin resistant,[10] this agent was often combined with an aminoglycoside for treatment. The First Neonatal Meningitis Cooperative Study Group evaluated intrathecal use of aminoglycosides compared to systemic delivery.[17] No advantage was demonstrated for local instillation of the drug into cerebrospinal fluid. The Second Neonatal Meningitis Cooperative Study Group evaluated intraventricular injection of aminoglycosides to supplement parenteral ampicillin therapy in contrast to systemic ampicillin plus gentamicin.[18] Again, no advantage was demonstrated for direct inoculation of drug. Because therapy was delivered by repeated ventricular punctures, the procedure seemed to result in excess risk related to the drug delivery.

Despite these findings, injection of supplemental aminoglycoside antibiotics into the central nervous system remains controversial.[19] Advocates employ an effective delivery system and note high rates of success.[20] Opponents feel that direct toxicity from local instillation is unwarranted.[21] Throughout this controversy the mainstay of treatment in neonatal Gram negative bacillary meningitis has remained parenteral ampicillin and gentamicin. The preferred therapeutic course for adults has varied from center to center.

Chloramphenicol use for Gram negative bacillary meningitis has been surrounded by similar controversy. Chloramphenicol inhibits but does not kill many Gram negative organisms.[22] Remarkably high infusion rates were required to achieve bactericidal effect in the rabbit model, producing levels of drug that would clearly be toxic for humans.[23] Yet chloramphenicol, alone or in combination with other antibiotics, has been frequently used to treat Gram negative bacillary meningitis. Cherubin et al. reported 89% mortality when chloramphenicol was employed as the only therapeutic agent in *E. coli* meningitis and 76% mortality when chloramphenicol was combined with other antibiotics.[4] Yet Berk and McCabe report 12 survivors among 16 patients treated with chloramphenicol[10] and Mangi et al. cured six of seven patients with Gram negative bacillary meningitis using this drug.[11] A survey of members of the Infectious Diseases Society of America showed common use of chloramphenicol. Successful outcome occurred in 69% of 16 patients treated with chloramphenicol alone, and 65% of 17 patients treated with chloramphenicol plus an aminoglyco-

side.[16] It is clear that "traditional therapy" is anything but traditional for Gram negative bacillary meningitis in adults.

First Generation Cephalosporin Treatment of Meningitis

Cephalothin and cephaloridine were advocated for and used in treatment of meningitis, but, as previously noted with chloramphenicol, the amount of drug required to kill most Gram negative bacilli is large.[24] Experimental studies and clinical trials documented relatively poor penetration of cephalothin into cerebrospinal fluid[25,26] and unfavorable patient outcome. Local inactivation of the drug in part accounted for the loss of activity.[27] Nephrotoxicity and lack of significant activity by weight precluded extensive use of cephaloridine. Despite the accumulation of substantial evidence against their clinical use, these drugs continued to be employed.[28] There is currently no role for first generation cephalosporins in the treatment of meningitis whatever its etiology.

Second Generation Cephalosporins in Treatment of Meningitis

Cefamandole was thought to be a potential advance in the treatment of meningitis. Animal studies yielded both favorable[13,29] and unfavorable[23] results. Clinical trials were originally promising,[30] but the report of three failures with susceptible strains that did not respond to treatment ended further evaluation of the compound.[31]

Cefoxitin did not undergo extensive clinical evaluation in the treatment of bacterial meningitis. The antibiotic does penetrate the central nervous system, particularly in the presence of inflammation.[32] Case reports have indicated that a successful outcome is possible, but insufficient data are available to endorse the use of cefoxitin in treatment of patients suspected or known to have meningitis.[33]

Cefuroxime is a new cephalosporin antibiotic that will soon become available for use in the United States. It has excellent *in vitro* activity against the major pathogens causing meningitis. Thirty of 30 infants in one study[34] and 18 of 21 children or adults treated with cefuroxime in a second study[35] had a satisfactory clinical and bacteriologic outcome. In the latter study, results compared favorably with ampicillin plus chloramphenicol treatment. Among cephalosporins generally categorized as second generation, cefuroxime currently has the best potential for treatment of bacterial meningitis caused by *S. pneumoniae, H. influenzae,* and *N. meningitidis*.

Third Generation Cephalosporins in Treatment of Meningitis

The newest cephalosporin antibiotics show exceptional activity *in vitro* against most Gram negative bacilli.[36] Numerous studies were performed in animals because these compounds seemed to offer a real potential for advance in the treatment of Gram negative bacillary meningitis. Schaad et al.[14] evaluated moxalactam in the treatment of meningitis caused by *E. coli, K. pneumoniae, Salmonella saint-paul,* and *Citrobacter diversus.* Excellent bactericidal activity was demonstrated in cerebrospinal fluid, and superiority was suggested over ampicillin and netilmicin. Schaad and colleagues also studied moxalactam, cefotaxime, cefoperazone, and ceftriaxone in the treatment of *E. coli* and group B Streptococcus type III meningitis.[37] Moxalactam had less activity than the other agents against the streptococcus. All four compounds were rapidly bactericidal against *E. coli.*

Perfect and Durack compared cefoperazone, moxalactam, cefotaxime, and trimethoprim-sulfamethoxazole kinetics in experimental meningitis caused by *H. influenzae.*[38] Trimethoprim-sulfamethoxazole penetrated noninflamed meninges better than the other agents, but all agents penetrated inflammed meninges relatively well. They proposed that concentrations achieved should provide therapeutic efficacy. Nolan and Ulmer evaluated cefotaxime and moxalactam in experimental *E. coli* meningitis.[39] Neither was taken up or metabolized by the choroid plexus. Systemic desacetylation by the liver resulted in lower cerebrospinal fluid concentrations of cefotaxime, but the combined activity of the parent compound plus the desacetyl metabolite produced rates of killing analagous to those achieved with moxalactam therapy.

McCracken et al.[40] compared cefoperazone, cefuroxime, ceftriaxone, and moxalactam in experimental *S. pneumoniae* and *H. influenzae* meningitis, and pointed out potential limitations in the clinical application of second and third generation cephalosporins for meningitis. Cefoperazone and ceftriaxone produced excellent bacterial killing in both infections. Moxalactam was effective only against *H. influenzae,* and cefuroxime only against *S. pneumoniae.* Finally, Sakata, et al.[41] evaluated ceftazidime in the treatment of pneumococcal, *H. influenzae* and *E. coli* meningitis. Results were favorable for all three pathogens, adding another cephalosporin to the list of potentially useful third generation compounds.

Clinical trials were initiated once it became apparent that experimental meningitis could be successfully treated. Dr. Nelson has reported results

of some of his studies in this issue of the *Bulletin*. Many other reports have been published. Most studies were noncomparative open trials and have been previously summarized.[33,42] The overall response rate has been unequivocally very favorable.

Premarketing clinical data from cefotaxime treatment of meningitis has been collected with the help of Drs. Charles Cherubin and John Kosola, and summarized in Table I. Among patients who received concurrent therapy, the agent had either not proved effective at the time cefotaxime was added or the concurrent therapy was added to cefotaxime because the responsible physician did not want to employ an investigational drug as the only therapeutic agent. Cefotaxime has shown excellent activity against both Gram positive and Gram negative pathogens.

Premarketing data for moxalactam has been collected with the assistance of Dr. Robert Kammer and summarized in Table II. A total of 205 patients were treated with moxalactam, and 41 of these were 15 years of age or older. Prior to initiation of therapy, 22 were considered to be in fair condition, 84 serious, and 91 critically ill. Only 13 deaths were reported, for a mortality rate of 6%. Although success was observed in the two cases of meningitis caused by Gram positive cocci, moxalactam is not indicated for treatment of these pathogens and is approved for Gram negative bacillary meningitis only. Pneumococcal meningitis developing while a patient was receiving moxalactam therapy has been described.

Cherubin has been collecting data on cefotaxime therapy of meningitis after release of the compound by the Food and Drug Administration (personal communication). Postmarketing results are summarized in Table III. Although the data have not been collected in a rigorously controlled fashion, the compound continues to produce excellent clinical results.

Additional clinical information suggests that other third generation cephalosporins will be highly effective. Ceftriaxone has been shown to penetrate into cerebrospinal fluid in adequate concentrations[43,44] and to be therapeutically effective.[45] Ceftazidime also achieved potentially therapeutic concentrations among 11 patients with meningitis being treated with other therapeutic agents.[46] Results of clinical trials have not yet been reported with this drug. Cefoperazone penetration into cerebrospinal fluid may be erratic,[47] although clinical success has been reported with this compound.[48] In sum, treatment of bacterial meningitis using third generation cephalosporins has had unprecedented success. Although more information is required, these compounds seem to be a significant therapeutic advance.

TABLE I. SPECTRUM OF PATHOGENS AND CLINICAL OUTCOME OF PATIENTS WITH MENINGITIS TREATED WITH CEFOTAXIME PRIOR TO 1982

Organism	*Number of patients*	*Number cured*	*Concurrent therapy*
The major pathogens:			
S. pneumoniae	14	14	2
N. meningitidis	22	22	4
H. influenzae	19	18	4
Other Gram positive organisms:			
S. aureus/epidermidis	7	4	6
Streptococci	5	3	3
Subtotal	67	61 (91%)	
Gram negative bacilli:			
E. coli	23	22	9
Klebsiella spp.	14	14	4
Enterobacter spp.	4	2	2
Serratia marcescens	6	6	3
Salmonella spp	7	4	0
Subtotal	51	46 (90%)	
Total	118	109 (91%)	

REPORTS OF FAILURE, THIRD GENERATION CEPHALOSPORINS

Schaad et al. reviewed reasons for failure of antimicrobial agents effectively to treat susceptible organisms.[49] Bacteria may reappear in cerebrospinal fluid during therapy (recrudescence) or within three weeks after therapy is stopped (relapse). Relapse is usually ascribed to persistence of infection in meningeal or parameningeal foci, and penetration of antibiotics into brain tissue may be important in preventing relapse.[50]

It is not surprising that cases of failure should be reported. Iannini and Kunkel described recrudescence of group A streptococcal meningitis during cefotaxime therapy.[51] The patient responded to treatment with penicillin G. Bradsher reported a patient with meningitis due to *Klebsiella pneumoniae*.[52] Five days after discontinuing therapy with cefotaxime, the patient relapsed with the same organism. Boughton et al. described a neonate with *E. coli* meningitis who relapsed 11 days after completing a three-week course of moxalactam therapy.[53] The authors speculated that antimicrobial failure was most likely due to sequestration of bacteria at an inaccessible ventricular or paraventricular focus.

The overall record of third generation cephalosporin treatment of bacterial meningitis remains exceptional. No antimicrobial compound can possibly be a panacea for this life threatening infection. Although initial

TABLE II. SPECTRUM OF PATHOGENS AND CLINICAL OUTCOME OF PATIENTS WITH MENINGITIS TREATED WITH MOXALACTAM THROUGH 1982

Organism	*Number of patients*	*Number cured*
The major pathogens:		
S. pneumoniae	1	1
N. meningitidis	3	3
H. influenzae	88	88
Other Gram positives organisms:		
S. aureus/epidemidis	1	1
Streptococci	0	0
Subtotal	93	93 (100%)
Gram negative bacilli:		
E. coli	24	23
Klebsiella spp.	24	23
Enterobacter spp.	9	9
Serratia marcescens	11	10
Salmonella spp.	1	1
Subtotal	69	66 (96%)
Total	162	159 (98%)

enthusiasm for first and second generation cephalosporins was great, only to be followed by identification of significant flaws in these compounds, the third generation cephalosporins have received closer scrutiny and more extensive clinical evaluation than any cephalosporin predecessors. The likelihood of disappointment seems very small.

THIRD GENERATION CEPHALOSPORINS: CONTROVERSIAL ISSUES AND POTENTIAL PROBLEMS

Several of the third generation cephalosporins, including cefotaxime, ceftizoxime, and ceftriaxone, have excellent *in vitro* activity against the pneumococcus. Most authorities consider pencillin G the drug of choice for pneumococcal meningitis. Yet penicillin penetration into cerebrospinal fluid is relatively poor.[54] The pneumococcus has shown a trend toward increased penicillin resistance for more than 10 years,[55] and mortality from pneumococcal meningitis has not changed during the past 30 years despite significant advances in supportive care.[56,57] It is legitimate to question whether penicillin should remain the drug of choice. An agent such as cefotaxime could potentially offer advantages if shortcomings in drug distribution and susceptibility account for treatment failures. Alternatively, maximal therapeutic benefit may be derived from current treatment

TABLE III. SPECTRUM OF PATHOGENS AND CLINICAL OUTCOME OF PATIENTS WITH MENINGITIS TREATED WITH CEFOTAXIME, 1982 TO DATE

Organism	*Number of patients*	*Number cured*
The major pathogens:		
S. pneumoniae	10	10
N. meningitidis	1	1
H. influenzae	2	2
Other Gram positive organisms:		
S. aureus/epidermidis	1	1
Streptococci	2	1
Subtotal	16	15 (94%)
Gram negative bacilli:		
E. coli	3	3
Klebsiella spp.	11	9
Enterobacter spp.	5	2
Serratia marcescens	4	4
Salmonella spp.	0	0
Subtotal	23	18 (78%)
Total	39	33 (85%)

patterns with penicillin, and mortality may not be further reducible without earlier diagnosis or changes in host defenses. It is of interest that the second most common pathogen causing meningitis and treated with cefotaxime by infectious diseases specialists since the release of this compound has been the pneumococcus (Table III).

In treatment of meningitis when the etiologic agent is not known or not apparent on Gram stain, cefotaxime has the advantage of providing coverage against group B streptococci among infants and pneumococci in adults. If *Listeria monocytogenes* is considered a potential pathogen, ampicillin should be added. Similarly, if moxalactam is to be used for meningitis of unknown etiology, ampicillin should be added until the pathogen is identified. None of the third generation cephalosporins have significant activity against *Listeria*, while activity against Gram positive cocci is variable.

Finally, among Gram negative bacilli, concern must be expressed about *Enterobacter species*. I have evaluated moxalactam, ceftizoxime, ceftriaxone, and cefotaxime in the treatment of experimental meningitis caused by *Enterobacter aerogenes*. None of these agents produced significant *in vivo* killing of the pathogen. Cerebrospinal fluid concentrations of drug ranged from 25 to 85 fold in excess of the *in vitro* minimum bactericidal

concentration of the organism.[58] Clearly, some strains of Gram negative bacilli resist the bactericidal activity of the new cephalosporins, whatever the *in vitro* susceptibility results.

Future Directions

New compounds continue to be developed and evaluated in the treatment of meningitis. Aztreonam, a monobactam, possesses excellent *in vitro* activity against Gram negative bacilli, including *Pseudomonas*. Thienamycin has an extremely broad spectrum of activity, including both Gram positive and Gram negative organisms. Aztreonam and thienamycin both penetrate the inflamed meninges of experimentally infected animals. Thus, the number of agents available to treat meningitis should continue to expand. The days of 60% or 80% mortality from this infectious process should be behind us.

REFERENCES

1. Karandis, D. and Shulman, J. A.: Recent survey of infectious meningitis in adults. *Southern Med. J. 69:*449-57, 1976.
2. Fraser, D. W., Henke, C. E., and Feldman, R. A.: Changing patterns of bacterial meningitis in Olmstead County, Minnesota, 1935-1970. *J. Infect. Dis. 128:*300-07, 1973.
3. Fraser, D. W., Darby, C. P., Koehler, R. E., et al.: Risk factors in bacterial meningitis: Charleston County, South Carolina. *J. Infect. Dis. 127:*271-77, 1973.
4. Cherubin, C. E., Marr, J. S., Sierra, M. F., Becker, S.: Listeria and Gram-negative bacillary meningitis in New York City, 1972-1979. *Am. J. Med. 71:*199-209, 1981.
5. Magnussen, C. R.: Meningitis in adults. *N. Y. State J. Med. 80:*901-06, 1980.
6. Stein, J. A., DeRossi, R., and Neu, H. C.: Adult *Hemophilus influenzae* meningitis. *N. Y. State J. Med. 69:*1760-63, 1969.
7. Selman, D., and Siedes, J. M.: *Hemophilus influenzae* meningitis in adults. *N. Y. State J. Med. 58:*2031-36, 1958.
8. Eykyn, S. J., Thomas, R. D., and Phillips, I.: *Haemophilus influenzae* meningitis in adults. *Br. Med. J. 2:*463-65, 1974.
9. Carpenter, R. R., and Petersdorf, R. G.: The clinical spectrum of bacterial meningitis. *Am. J. Med. 33:*262-75, 1962.
10. Berk, S. L. and McCabe, W. R.: Meningitis caused by Gram-negative bacilli. *Ann. Intern. Med. 93:*253-60, 1980.
11. Mangi, R. J., Quintiliani, R., and Andriole, V. T.: Gram-negative bacillary meningitis. *Am. J. Med. 59:*829-36, 1975.
12. Dacey, R. G., and Sande, M. A.: Effect of probenecid on cerebrospinal fluid concentrations of penicillin and cephalosporin derivatives. *Antimicrob. Agents Chemother. 6:*437-40, 1974.
13. Beam, T. R., and Allen, J. C.: Blood, brain and cerebrospinal fluid concentrations of several antibiotics in rabbits with intact and inflamed meninges. *Antimicrob. Agents Chemother, 12:*710-16, 1977.
14. Schaad, U. B., McCracken, G. H., Loock, C. A., and Thomas, M. L.: Pharmacokinetics and bacteriologic efficacy of moxalactam (LY 127935), netilmicin, and ampicillin in experimental Gram-negative enteric bacillary meningitis. *Antimicrob. Agents Chemother. 17:*406-11, 1980.
15. Beam, T. R., and Mylotte, J. M.: Interrelations Between Host Defenses and

Antibiotics in Experimental Meningitis in Rabbits. *17th Int. Annual National Meeting of the Reticuloendothelial Society*, 1980.
16. Rahal, J. J. and Simberkoff, M. S.: Host defenses and antimicrobial therapy in adult Gram-negative bacillary meningitis. *Ann. Int. Med. 96:*468-74, 1982.
17. McCracken, G. H., Jr., and Mize, S. G.: A controlled study of intrathecal antibiotic therapy in Gram negative enteric meningitis of infancy. *J. Pediatr. 89:*66-72, 1976.
18. McCracken, G. H., Jr., Mize, S. G., and Threlkeld, N.: Intra-ventricular gentamicin therapy in Gram negative bacillary meningitis of infancy. *Lancet 1:*787-91, 1980.
19. Swartz, M. N.: Intraventricular use of aminoglycosides in the treatment of Gram-negative bacillary meningitis: Conflicting views. *J. Infect. Dis. 143:*293-96, 1981.
20. Wright, P. F., Kaiser, A. B., et al.: Trijillo, H. and McGee, Z. A.: The pharmacokinetics and efficacy of an aminoglycoside administered into the cerebral ventricles in neonates: implications for further evaluation of this route of therapy in meningitis.: *J. Infect. Dis. 143:* 141-47, 1981.
21. Hodges, G. R., Watanabe, I., Singer, P., et al.: Central nervous system toxicity of intraventricularly administered gentamicin in adult rabbits. *J. Infect. Dis.* 1981; *143:*148-55, 1981.
22. Rahal, J. J., Jr., and Simberkoff, M. S.: Bactericidal and bacteriostatic action of chloramphenicol against meningeal pathogens. *Antimicrob. Agents Chemother, 16:*13-18, 1979.
23. Beam, T. R. and Allen, J. C.: Comparison of cefamandole, cephalothin, ampicillin and chloramphericol in experimental *Escherichia coli* meningitis. *Antimicrob. Agents Chemother, 17:*37-42, 1980.
24. Turck, M., Belcher, D. W., Ronald, A.: New cephalosporin antibiotic - cephaloridine. clinical and laboratory evaluation. *Arch. Int. Med. 119:*50-59, 1967.
25. Brown, J. D., Mathies, A. W., Jr., Ivler, D., et al.: Variable results of cephalothin therapy for meningococcal meningitis. *Antimicrob. Agents Chemother.* 432-40, 1970.
26. Mangi, R. J., Kundargi, R. S., Quintiliani, R., and Andriole, V. T.: Development of meningitis during cephalothin therapy. *Ann. Intern. Med. 78:*347-51, 1973.
27. Nolan, G. M., Ulmer, and W. C., Jr.: A study of cephalothin and descetylcephalothin in cerebrospinal fluid in therapy for experimental pneumococcal meningitis. *J. Infect. Dis. 141:*326-30, 1980.
28. Fisher, L. S., Chow, A. W., Yoshikawa, T. T., and Guze, L. B.: Cephalothin and cephaloridine therapy for bacterial meningitis. *Ann. Intern. Med. 82:*689-93, 1975.
29. Sande, M. A., Sheretz, R. J., Zak, O., and Strausbaugh, L. J.: Cephalosporin antibiotics in the therapy of experimental *Streptococcus pneumoniae* and *Haemophilus influenzae* meningitis in rabbits. *J. Infect. Dis. 137* (Suppl.):S161-68, 1978.
30. Korzeniowski, O. M., Carvalho, E. M., Jr., Rocha, H., and Sande, M. A.: Evaluation of cefamandole therapy of patients with bacterial meningitis. *J. Infect. Dis. 137* (Suppl.):S169-79, 1978.
31. Steinberg, E. A., Overturf, G. D., Wilkins, T., et al.: Failure of cefamandole in the treatment of meningitis due to *Haemophilus influenzae* type B. *J. Infect. Dis. 137* (Suppl.):S180-86, 1978.
32. Richards, M. L., Prince, R. A., Kenaley, K. A., et al.: Antimicrobial penetration into cerebrospinal fluid. *Drug Intell. Clin. Pharm. 15:*341-68, 1981.
33. Landesman, S. H., Corrado, M. L., Shah, P. M., et al.: Past and current roles for cephalosporin antibiotics in treatment of meningitis. *Am. J. Med. 71:*693-703, 1981.
34. Pfenninger, J. Schaad, U. B., Lutschg J., et al.: Cefuroxime in bacterial meningitis. *Arch. Dis. Child. 57:*539-43, 1982.
35. Swedish Study Group: Cefuroxime verusus ampicillin and chloramphenicol for the treatment of bacterial meningitis. *Lancet 1:*295-99, 1982.
36. Beam, T. R.: The third generation of cephalosporins. *Rat. Drug Therapy 16:*1-7, *16:*1-6, 1982.

37. Schaad, U. B., McCracken, G. H., Jr., Loock, C. A., and Thomas M. L.: Pharmacokinetics and bacteriologic efficacy of moxalactam, cefotaxime, cefoperazone, and rocephin in experimental bacterial meningitis. *J. Infect. Dis. 143:* 156-63, 1981.
38. Perfect, J. R., and Durack, D. T.: Pharmacokinetics of cefoperazone, moxalactam, cefotaxime, trimethoprim and sulfamethoxazole in experimental meningitis. *J. Antimicrob. Chemother. 8:* 49-58, 1981.
39. Nolan, C. M., and Ulmer, C., Jr.: Penetration of cefotaxime and moxalactam into cerebrospinal fluid of rabbits with experimentally induced *Escherichia coli* meningitis. *Rev. Infect. Dis. 4* (Suppl.): S396-S400, 1982.
40. McCracken, G. H., Jr., Nelson, J. D., and Grimm, L.: Pharmacokinetics and bacteriologic efficacy of cefoperazone, cefuroxime, ceftriaxone and moxalactam in experimental *Streptococcus pneumoniae* and *Haemophilus influenzae* meningitis. *Antimicrob. Agents Chemother. 21:* 262-67, 1982.
41. Sakata, Y., Boccazzi, A., and McCracken, G. H., Jr.: Pharmacokinetics and bacteriologic effect of ceftazidime in experimental *streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* meningitis. *Antimicrob. Agents Chemother, 23:* 213-17, 1983.
42. Cherubin, C. E., Corrado, M. L., Nair, S. R., et al.: Treatment of Gram-negative bacillary meningitis: Role of the new cephalosporin antibiotics. *Rev. Infect. Dis. 4* (Suppl.): S453-64, 1982.
43. Latif, R. and Dajani, A. S.: Ceftriaxone diffusion into cerebrospinal fluid of children with meningitis. *Antimicrob. Agents Chemother. 23:* 46-48, 1983.
44. Steele, R. W., Eyre, L. B., Bradsher, R. W., et al.: Pharmacokinetics of ceftriaxone in pediatric patients with meningitis. *Antimicrob. Agents Chemother. 23:* 191-94, 1983.
45. Cadoz, M., Denis, F., Felix, H., and Diop, I.: Treatment of purulent meningitis with a new cephalosporin - rocephin (RO 13-9904) clinical and bacteriological observations in 24 cases. *Chemotherapy 27* (Suppl.): 57-61, 1981.
46. Modai, J., Vittecq, D., DeCazes, J. M., et al.: Penetration of ceftazidime into cerebrospinal fluid of patients with bacterial meningitis. *Antimicrob. Agents Chemother. 24:* 126-28, 1983.
47. Cable, D., Overturf, G., and Edralin, G.: Concentrations of cefoperazone in cerebrospinal fluid during bacterial meningitis. *Antimicrob. Agents Chemother 23:* 688-91, 1983.
48. Pegler, R.B.E. and Lang, S.D.R.: Cefoperazone in klebsiella meningitis: a case report. *Drugs 22* (Suppl.): 69-71, 1981.
49. Schaad, U. B., Nelson, J. D., and McCracken, G. H., Jr.: Recrudescence and relapse in bacterial meningitis of childhood. *Pediatrics 67:* 188-95, 1981.
50. Beam T. R., and Allen, J. C.: Assessing antibiotic efficacy in acute bacterial meningitis. *Clin. Pharmacol. Ther. 25:* 199-203, 1979.
51. Iannini, P. B. and Kunkel, M. J.: Cefotaxime failure in Group A Streptococcal meningitis. *J.A.M.A. 248:* 1878, 1982.
52. Bradsher, R. W.: Relapse of Gram-negative bacillary meningitis after cefotaxime therapy. *J.A.M.A. 248:* 1214-15, 1982.
53. Broughton, R. A., Mason, E. O., and Baker, C. J.: Relapse of *Echerichia coli* meningitis following therapy with moxalactam. *Pediatr. Infect. Dis. 1:* 24-28, 1982.
54. Hieber, J. P. and Nelson, J. D.: A pharmacologic evaluation of penicillin in children with purulent meningitis. *N. Engl. J. Med. 297:* 410-13, 1977.
55. Hansman, D., Glasgow, H., Sturt, J., et al.: Increased resistance to penicillin of pneumococci isolated from man. *N. Engl. J. Med. 284:* 175-77, 1971.
56. Hodges, G. R. and Perkins, R. L.: Acute bacterial meningitis: An analysis of factors influencing prognosis. *Am. J. Med. Sci. 270:* 427-40, 1975.
57. Center for Disease Control: Bacterial Meningitis and Meningococcemia - United States, 1978. *Morb. Mort. Weekly Rep. 28:* 277-79, 1979.
58. Beam, T. R.: Antibiotic failure in experimental meningitis. *Proceedings 13th International Cong. Chemother. 81:* 12-14, 1983.